

REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Claim 9 has been amended to clarify that anergized CD4⁺ CD25⁻ T cells are obtained by contacting the CD4⁺ CD25⁻ T cells with *activated* CD4⁺ CD25⁺ T cells *ex vivo* or *in vivo*. This language finds support throughout the entire specification. See, for example, the last two sentences in the second paragraph on page 1 (“... CD4⁺ CD25⁺ T cells ... inhibit the proliferation of CD4⁺ and CD8⁺ T cells *after stimulation* via their TCR ...”); the third sentence of the second paragraph on page 2 (“... CD4⁺ CD25⁺ T cells ... need ... *activation* via their TCR to suppress other T cells”); the middle of page 8, also teaching that CD4⁺ CD25⁺ T cells require direct cell contact and stimulation via the TCR to suppress unwanted T cell activation; and the instant examples, particularly, Example 1, showing activation of CD4⁺ CD25⁺ T cells by treatment with plate-bound anti-CD3 and soluble anti-CD28 or with mature allogeneic dendritic cells. New claims 37 and 38 are drawn to these same activation methods and are, therefore, also supported by Example 1.

Claims 11, 35 and 36 have been amended to make clear that the CD4⁺ CD25⁺ T cells mentioned in these claims are the same CD4⁺ CD25⁺ T cells mentioned in main claim 9.

Applicants do not believe that any of the amendments above introduce new matter. An early notice to that effect is earnestly solicited.

Claims 9, 11, 29, 30, 35 and 36 were rejected under 35 USC § 112, first paragraph, as claiming new matter. In response, Applicants again rely on original claim 4 and Examples 4 and 5, and, additionally, on original claims 9 and 10. The Examiner is correct that original claim 4 pertains to isolated Tr1-like regulatory cells and not to a method of obtaining such cells by anergizing CD4⁺ CD25⁻ T cells by contact with CD4⁺ CD25⁺ T cells. However, Applicants point out that original claim 9 references the isolated Tr1-like regulatory cells of original claim 4 and specifies that these cells can be produced by anergizing CD4⁺ CD25⁻ T cells by contacting the CD4⁺ CD25⁻ T cells with an anergic state inducing agent. Original claim 10, in turn, refers to original claim 9 and specifies in clause (i) that the anergic state inducing agent comprises CD4⁺ CD25⁺ T cells. Thus, there is support in the original application in the form of the combination of original claims 4, 9 and 10 that isolated Tr1-like regulatory cells can be obtained by anergizing CD4⁺ CD25⁻ T cells by contacting the CD4⁺ CD25⁻ T cells with activated CD4⁺ CD25⁺ T cells. Further, a person having ordinary skill in the art would understand that in order for the Tr1-like regulatory cells to be isolated after such contact, it is necessary for the anergized CD4⁺ CD25⁻ T cells to be separated from the CD4⁺ CD25⁺ T cells. CD4⁺ CD25⁻ T cells anergized by contact with CD4⁺ CD25⁺ T cells cannot be isolated unless separated from the CD4⁺ CD25⁺ T cells. Consequently, the instant specification does, in fact, provide support for “separating.” Further on this point, Applicants remind the Examiner that satisfaction of the written description requirement does not require *ipsis verbis* support for “separating.” See, e.g., *In re Anderson*, 176 USPQ 331, 336 (CCPA 1973), for the proposition that in determining whether an amendment to a claim constitutes new matter, the question is not whether the added word

is a word that is used in the application as filed, but whether the concept embodied by the added word is present in the original specification. As explained above, the original application supports the concept of separating anergized CD4⁺ CD25⁻ T cells from CD4⁺ CD25⁺ T cells. Therefore, Applicants' use of the term "separating" does not introduce new matter.

Further, Applicants take issue with the Examiner's overly restrictive reading of Examples 4 and 5. Examples are intended to be just that—exemplary. A person having ordinary skill in the art would read those examples in the context of the broader disclosure as providing a teaching that generally anergized CD4⁺ CD25⁻ T cells separated from the contacting CD4⁺ CD25⁺ T cells are useful to suppress proliferation of syngeneic CD4⁺ CD25⁻ T cells mediated by IL-10.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Claims 9, 11, 29, 30, 35 and 36 were rejected under 35 USC § 102(b) as being anticipated by Baecher-Allan et al. ("Baecher-Allan"), *J. Immunol.*, 167: 1245-1253 (2001). In response, Applicants respectfully submit that Baecher-Allan does not teach anergizing CD4⁺ CD25⁻ T cells by contacting the CD4⁺ CD25⁻ T cells with *activated* CD4⁺ CD25⁺ T cells *ex vivo* or *in vivo* to yield human Tr1-like regulatory cells; and thereafter separating the human Tr1-like regulatory cells from the CD4⁺ CD25⁺ T cells, as required by the instant claims.

While the Examiner appears to be correct that Baecher-Allan teaches incubating PBMC with anti-CD4 and anti-CD25 antibodies, Applicants respectfully submit that this is just for sorting and is not activating. In other words, although CD4⁺ CD25⁺ T cells and CD4⁺ CD25⁻ T cells can both be found in human blood, the CD4⁺ CD25⁻ T cells have not necessarily been anergized by any contact with the CD4⁺ CD25⁺ T cells because the CD4⁺ CD25⁺ T cells have not necessarily been activated at the time of any such contact. Applicants point to the discussion above concerning the support for the amendments to claim 9: In order for the CD4⁺ CD25⁺ T cells to exercise their regulatory capabilities, these cells need to be in contact with other T cells and also activated. Baecher-Allan teaches in the legend for Figure 1 on page 1247 that *post-separation* activation was brought about using plate-bound anti-CD3. The fact that Baecher-Allan was required to activate these CD4⁺ CD25⁺ T cells proves they were not necessarily activated when they were isolated from PBMC and sorted in spite of the fact that the CD4⁺ CD25⁺ T cells may have been in contact with CD4⁺ CD25⁻ T cells in the blood. This also proves that neither CD4⁺ CD25⁺ T cells nor CD4⁺ CD25⁻ T cells are necessarily activated by contacting these cells with either anti-CD4 or anti-CD25 antibodies to isolate and/or to sort them.

Nowhere does Baecher-Allan describe the specific combination of steps required by the instant claims, i.e., that Tr1-like regulatory cells are produced by (a) anergizing CD4⁺ CD25⁻ T cells by contacting the CD4⁺ CD25⁻ T cells with CD4⁺ CD25⁺ T cells *ex vivo* or *in vivo* to yield human Tr1-like regulatory cells; and then (b) separating the human Tr1-like regulatory cells from the CD4⁺ CD25⁺ T cells. This is true not only of the experiments described in the Figure 1 legend, but also of the experiments described

on page 1246 of Baecher-Allan, particularly relied on by the Examiner at the top of page 4 of the outstanding Office Action, and, indeed, throughout the reference. In several instances (e.g., page 1247, right column, first paragraph; page 1249, right column), Baecher-Allan describes cocultures of CD4⁺ CD25⁺ and CD4⁺ CD25⁻ T cells that are stimulated (e.g., with anti-CD3), but in all of those instances, the cells are analyzed *without separation*.

This is not surprising inasmuch as Applicants respectfully submit that Baecher-Allan's focus is on the CD4⁺ CD25⁺ T cells and their ability to inhibit proliferation and cytokine secretion by activated CD4⁺ CD25⁻ responder T cells. Instant Applicants were the first to focus attention on the anergized CD4⁺ CD25⁻ T cells themselves and to recognize that these anergized CD4⁺ CD25⁻ T cells had suppressive properties themselves and, therefore, could be used to suppress the proliferation of CD4⁺ T cells. Thus, again, Baecher-Allan does not teach or suggest separation after anergizing of Tr1-like regulatory cells from anergizing activated CD4⁺ CD25⁺ T cells, as required by the instant claims.

In view of the foregoing, Applicants respectfully submit that Baecher-Allan does not anticipate the present claims. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well.

Claims 9, 11, 29, 30, 35 and 36 were rejected under 35 USC § 102(a) as being anticipated by Jonuleit et al. ("Jonuleit"), *J. Exp. Med.*, 196: 255-260 (2002). In response, Applicants respectfully submit that the present record evidences that Jonuleit is not prior art to the present application.

On page 6 of the Office Action dated April 20, 2006, the Examiner rejected claims 9-11, 29 and 30 as being anticipated by Dieckmann et al. ("Dieckmann"), *J. Exp. Med.*, 196: 247-253 (2002). The Examiner will recognize that both Dieckmann and Jonuleit appeared in the same July 15, 2002 issue of the *Journal of Experimental Medicine*.

In response to the anticipation rejection based on Dieckmann, Applicants submitted a declaration of the instant inventors on October 20, 2006. In numbered paragraph 4 of that declaration the instant inventors confirmed that what was disclosed in the Dieckmann article was their own invention.

Applicants refer the Examiner's attention to the middle of the right-hand column on page 252 of the Dieckmann article. There is the indication that the article was submitted on April 22, 2002, and accepted on June 5, 2002, without revision.

Applicants now refer the Examiner's attention to the bottom of the right-hand column on page 259 of Jonuleit. There is the indication that the Jonuleit article was also accepted on June 5, 2002, after revision.

The foregoing shows that the present inventors had possession of the present invention, as disclosed in the Dieckmann article, at least as early as April 22, 2002, when they submitted the article to the *Journal of Experimental Medicine*. Since the article was accepted without revision, everything in the published article was also present in that original submission on April 22, 2002.

On the other hand, the Jonuleit article could not have been published prior to June 5, 2002, as this was the date on which the Jonuleit article was finally accepted by the *Journal of Experimental Medicine*.

In short, the evidence of record shows that the present inventors had the present invention at least as early as April 22, 2002, whereas the Jonuleit article could not have been published until after June 5, 2002. Therefore, the Jonuleit article cannot be prior art to the instant invention or, therefore, the instant application.

In view of the foregoing, Applicants respectfully submit that the Jonuleit article is not prior art to the instant claims. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,

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